

Extranodal NK/T-cell lymphoma presenting as a pituitary mass

Case report and review of the literature

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✓Primary pituitary lymphomas (PPLs) are rare tumors of the central nervous system, and most are of B-cell origin. Extranodal NK/T-cell lymphomas are uncommon neoplasms that are highly aggressive and show a strong association with Epstein–Barr virus. They most commonly affect the nasal cavity and paranasal sinuses; manifestation as a primary pituitary tumor has never been described. The authors report a case of NK/T-cell lymphoma of the pituitary gland and review 17 cases of PPL from the literature.

All patients had been evaluated at presentation for clinical, neuroimaging, and histopathological findings. Patients who had systemic lymphoma with secondary involvement of the pituitary gland were excluded. The mean patient age was 55.5 years (range 26–86 years); the male/female ratio was 13:5. The most common presentation was pituitary insufficiency (72%), followed by headache (56%), diplopia (39%), visual loss (28%), and fever (22%). Thirteen patients (72%) exhibited anterior hypopituitarism and seven (39%) had diabetes insipidus at presentation. Magnetic resonance imaging demonstrated enhancing parasellar masses with diffuse enlargement of the pituitary gland (94%), suprasellar extension (44%), cavernous sinus extension (39%), and stalk thickening (22%). Thirteen patients (72%) had B-cell lymphoma, four (22%) had T-cell lymphoma, and one (6%) had NK/T-cell lymphoma.

Primary pituitary lymphomas are rare entities with a range of clinical presentations and neuroimaging findings that are unique from those of patients who present with pituitary adenomas. The pathological entity of NK/T-cell lymphoma is distinct, and its course is very aggressive with a poor prognosis. (DOI: 10.3171/JNS-07/09/0660)

KEY WORDS • central nervous system lymphoma • pituitary tumor • primary pituitary lymphoma

PRIMARY CNS lymphomas account for less than 2% of all intracranial neoplasms.⁹ By definition, these tumors are extranodal and arise primarily in the craniospinal axis; they should not be confused with systemic lymphomas that secondarily metastasize to the CNS. Even more rare are PPLs. In one study the incidence of pituitary lymphoma among a large cohort of patients who underwent transsphenoidal surgery for sellar masses was noted to be less than 1%.¹⁰ During the past two decades, the number of cases of PPLs reported has increased.¹¹ Most PPLs are of B-cell origin on histopathological examination, although there are a few cases of PPLs of T-cell origin.

Extranodal NK/T-cell lymphomas are distinct pathological entities from B- or T-cell lymphomas; they have a highly aggressive course with poor prognosis. Although generally rare, these tumors are more common in people of Asian, Mexican, and South American descent. The lesions have a strong association with EBV. Histologically, the most common immunophenotype is CD2-positive, surface CD3-negative, cytoplasmic CD3-positive, and CD56-positive. Extranodal NK/T-cell lymphomas often affect the nasal cavity and other mucosal sites of the upper gastrointestinal tract. They frequently present in midline facial structures as nasal obstruction or midfacial destruction. Some cases of NK/T-cell lymphomas involving the CNS via direct extension from the nose have been reported, as has one case of primary brain NK/T-cell lymphoma;¹⁵ however, no primary NK/T-cell lymphomas arising from the pituitary gland have been reported previously. To the best of our knowledge, we report

Abbreviations used in this paper: CNS = central nervous system; CT = computed tomography; EBER = EBV-encoded RNA; EBV = Epstein–Barr virus; MR = magnetic resonance; PPL = primary pituitary lymphoma.

Primary pituitary lymphoma

the first case of extranodal NK/T-cell lymphoma presenting as a PPL. We present this unique case and also review 17 other cases of PPL found in the literature. The clinical presentation, neuroimaging characteristics, and histopathological features are discussed. We excluded patients who had systemic lymphoma with secondary involvement of the pituitary gland.

Case Report

History and Examination. This 26-year-old Hispanic man presented with a 2-week history of headaches associated with nausea and vomiting, which was then followed by worsening diplopia. On examination, the patient had a mild left sixth cranial nerve palsy. The remainder of his examination revealed normal findings.

A CT scan of the head without contrast revealed a hyperdense mass in the sellar and suprasellar region extending to the left side of the sella and cavernous sinus (Fig. 1). Magnetic resonance imaging of the brain (Fig. 2) demonstrated an enhancing sellar mass with suprasellar extension compressing the optic chiasm. The mass also involved the planum sphenoidale, anterior clinoid process, infundibulum, and clivus. There was also extension into bilateral cavernous sinuses with encasement of the cavernous carotid arteries bilaterally. There was dural enhancement adjacent to the anterior skull base, planum sphenoidale, and clivus.

A formal ophthalmological examination verified an incomplete left sixth cranial nerve palsy. An endocrinological evaluation revealed hypocortisolism, hypothyroidism, and hypotestosteronemia. The patient's serum prolactin level was slightly elevated at 22 ng/ml, consistent with stalk effect. Corticosteroid and thyroid hormone replacement was initiated to treat his hypopituitarism. The patient's erythrocyte sedimentation rate was elevated at 27 mm/hour, and he had fevers during his hospital course without any positive blood or cerebrospinal fluid cultures. A lymphoma of the pituitary gland was suspected, and a transnasal transsphenoidal biopsy of the mass was performed.

Operation. At surgery, tumor was seen at both sphenoid ostia. The face of the sphenoid sinus was opened widely, and the tumor within the sphenoid sinus was removed. Results of the initial preliminary frozen section revealed lymphoma. After removing the tumor in the sphenoid sinus, the sellar floor was incompetent and the sellar dura mater was opened. The mass in the sella appeared abnormal and a biopsy specimen was obtained. No further resection was performed because of the preliminary diagnosis of lymphoma.

Pathological Examination. Histological examination of both biopsy samples from the sphenoid and sella revealed a diffusely infiltrative mass involving the sphenoid sinus mucosa and pituitary gland (Fig. 3). The infiltrative cells were small- to medium-sized lymphocytes that were immunopositive for CD45 (leukocyte common antigen). Apoptotic cells were numerous, and occasional mitotic figures were also present. Angiocentric growth was not seen. Immunohistochemical staining showed the tumor cells to be negative for the B-cell marker CD20 and immunoreactive for the T-cell marker CD3 but in a cytoplasmic rather than surface pattern. Further marker studies showed the tumor cells to be positive for CD2 and CD56, indicating that this was an extranodal, nasal-type NK/T-cell lymphoma. Markers CD4, CD5, CD7, CD8, CD79a, CD30, TdT, and AE1/AE3 (pan-

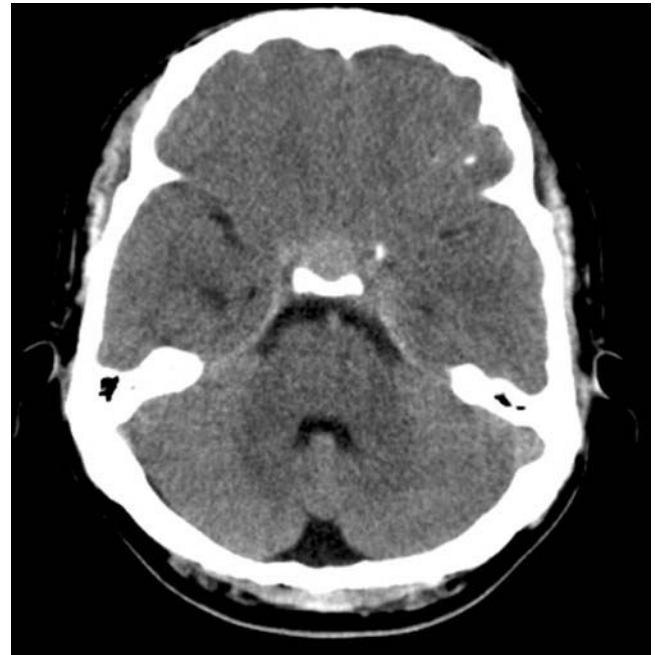


FIG. 1. A CT image of the head demonstrating a hyperdense mass in the sellar and suprasellar region extending to the left side of the sella.

cytokeratin) were negative. The tumor cells were also found to be strongly positive for EBERs.

Postoperative Course. Postoperatively, the patient remained stable, although he had transient diabetes insipidus, which resolved by the time of discharge from the hospital. The remainder of the hospital course was uneventful. The results of an HIV test were negative. Further metastatic workup included CT scans of the chest, abdomen, and pelvis, which did not reveal any masses. Bone marrow aspiration was negative for any evidence of malignancy. Isolated disease of the pituitary gland was diagnosed, and the patient was started on postoperative adjuvant radiation and chemotherapy.

The patient underwent fractionated intensity-modulated radiation therapy to the tumor site (25 fractions of 200 cGy for a total dose of 5000 cGy) followed by six cycles of hyper-CVAD chemotherapy (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) with intrathecal methotrexate and cytarabine. Follow-up MR imaging (Fig. 4) performed 5 months after surgery demonstrated a significant interval decrease in the size of the suprasellar and skull base mass, suggestive of a response to treatment. There was still residual enhancement seen in the left cavernous sinus and Meckel cave; however, a screening bone marrow biopsy demonstrated bone marrow invasion of NK/T-cell lymphoma. The patient was readmitted to undergo additional chemotherapy (cisplatin, etoposide, gemcitabine, methylprednisolone sodium succinate injection, and intrathecal cytarabine liposome). Four weeks later, the patient developed neutropenic fever and overwhelming infections and was found to have widespread dissemination of lymphoma to his liver. Given his poor prognosis, the patient was transferred to hospice care where he eventually died of the lymphoma.

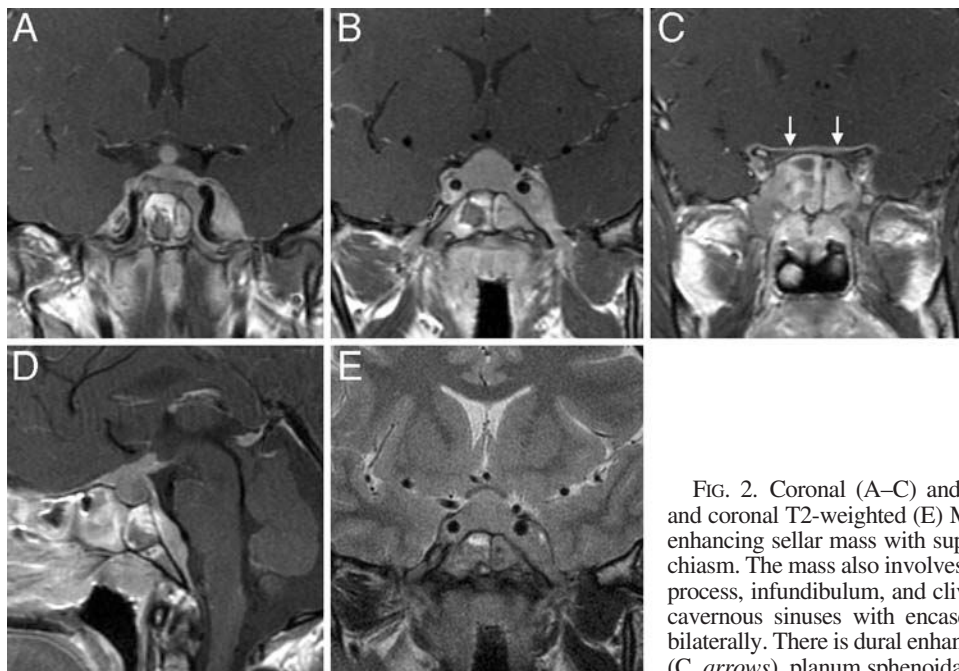


FIG. 2. Coronal (A–C) and sagittal (D) Gd-enhanced T1-weighted and coronal T2-weighted (E) MR images of the brain demonstrating an enhancing sellar mass with suprasellar extension compressing the optic chiasm. The mass also involves the planum sphenoidale, anterior clinoid process, infundibulum, and clivus. There is also extension into bilateral cavernous sinuses with encasement of the cavernous carotid arteries bilaterally. There is dural enhancement adjacent to the anterior skull base (C, arrows), planum sphenoidale, and clivus.

Results

From a survey of the literature, we identified 17 additional cases of PPL for a total review of 18 cases (Table 1). The mean age of patients was 55.5 years (range 26–86 years), and there was a 13:5 male/female ratio. The most common presentation was pituitary insufficiency (72%), followed by headache (56%), diplopia (39%), visual loss (28%), and fever (22%). Thirteen patients (72%) exhibited anterior hypopituitarism and seven (39%) had diabetes insipidus at presentation. Four (22%) had mild hyperprolactinemia from stalk compression effect. The MR images demonstrated enhancing parasellar masses with diffuse enlargement of the pituitary gland (94%), suprasellar extension (44%), cavernous sinus extension (39%), and stalk thickening (22%).

Thirteen patients (72%) had B-cell lymphoma, four (22%) had T-cell lymphoma, and one (6%) had NK/T-cell lymphoma.

Discussion

Primary Pituitary Lymphoma

Primary CNS lymphomas constitute approximately less than 2% of all intracranial neoplasms.⁸ Although these tumors have been known to be associated with immunocompromised conditions and AIDS, recent data have shown a significant increase in the incidence with immunocompetent patients.^{7,8,28} The incidence of PPL is very low; PPL was encountered in one (< 1%) of 1120 patients who underwent

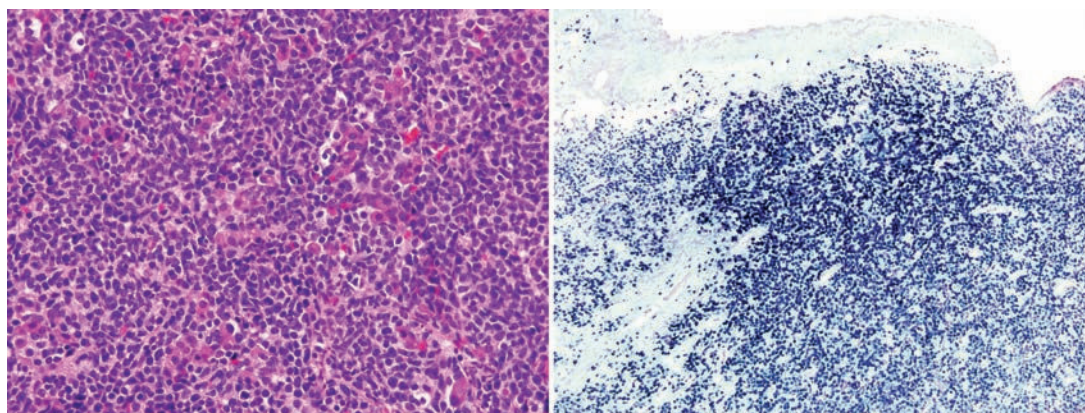


FIG. 3. Photomicrographs. *Left*: Examination of the pituitary mass stain demonstrating lymphoma cells infiltrating and effacing the pituitary gland. The larger cells with noticeable eosinophilic cytoplasm are entrapped anterior pituitary cells. H & E. *Right*: In situ hybridization for EBV-EBER. The tumor cells are strongly positive (blue nuclear staining), whereas the overlying epithelium and submucosal blood vessels are negative. Original magnification $\times 400$ (left) and $\times 200$ (right).

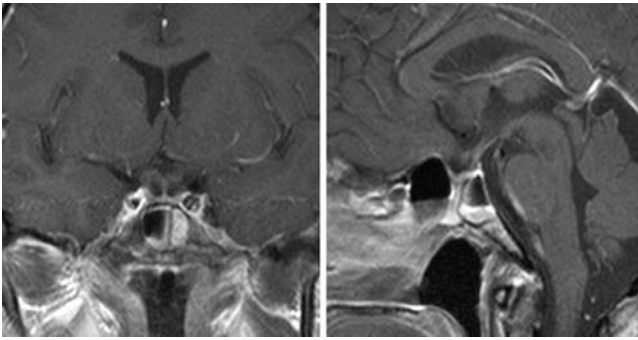


FIG. 4. Follow-up MR images obtained 5 months after surgery, chemotherapy, and radiation therapy, demonstrating significant interval decrease in size of the parasellar mass suggesting response to treatment. Residual enhancement is seen in the left cavernous sinus.

transsphenoidal resection for pituitary masses.¹⁰ The number of cases of primary lymphomas presenting as pituitary tumors reported in the literature seems to be increasing in recent years.¹⁰

In our review of 18 patients with PPL, we found that the mean age at presentation and male predominance were similar to those described in patients with primary CNS lymphomas. Patients in immunodeficient states and with PPL presented at a younger age. Endocrine abnormalities were strongly associated with PPL, and pituitary insufficiency was the most common presentation. Seventy-two percent of patients exhibited anterior hypopituitarism and 39% had

diabetes insipidus, which may result from involvement or compression of the pituitary stalk, hypothalamus, or paraventricular region of the third ventricle. The variety of endocrine abnormalities suggests different origins of lymphoproliferative tissue.¹¹ Clinically, patients with hypopituitarism presented with a variety of symptoms, including fatigue, muscle weakness, loss of libido, amenorrhea, thirst, and polyuria.

Headache was also a common presenting symptom (56%). Diplopia due to cavernous sinus compression of the cranial nerves was present in 39% of patients and visual field or acuity compromise was present in 28%. One patient had facial numbness in the first and second divisions of the trigeminal nerve and one patient had sensorineural hearing loss. Four patients (22%), including ours, presented with a fever of unknown origin.

Nonfunctioning pituitary adenomas typically appear with visual field and acuity compromise, signs of hypopituitarism, and nonspecific headaches. Although PPLs may present with similar symptoms, the presence of diabetes insipidus, cranial neuropathies resulting in diplopia, and fever of unknown origin should raise the suspicion of a nonadenomatous sellar/parasellar lesion, such as a lymphoma.¹¹ As many as 25% of patients with nonadenomatous sellar/parasellar lesions have impairment of the second, third, fourth, and sixth cranial nerves.¹⁰

The MR images demonstrated enhancing parasellar masses with diffuse enlargement of the pituitary (94%), suprasellar extension (44%), cavernous sinus extension (39%), and stalk thickening (22%). The MR images ob-

TABLE 1
*Clinical summary of 18 patients with PPL**

Authors & Year	Age (yrs), Sex	Clinical Presentation	Endocrine Abnormality	Coexisting Lesion	Origin
Singh et al., 1993	28, M	HA, visual loss, facial numbness	—	—	B-cell
Samuels & de la Monte, 1994	49, M	HA, SNHL, nystagmus, decreased libido	ant hypopit, DI, PRL	—	B-cell
Gottfredsson et al., 1996	48, M	HA, nausea/vomiting, meningismus, fever, diplopia (CN VI palsy)	—	—	B-cell
Shaw et al., 1997	73, F	HA, fatigue, diplopia (CN VI palsy), polyuria	ant hypopit, DI, PRL	—	B-cell
Li et al., 1998	77, M	generalized weakness	ant hypopit	—	B-cell
Sakakibara et al., 1998	53, M	HA, diplopia (CN VI palsy)	—	—	T-cell
Freda & Post, 1999	48, M	HA, diplopia (CN III, VI palsies)	—	—	B-cell
Kuhn et al., 1999	67, F	diplopia (CN III palsy), visual loss	ant hypopit	pituitary adenoma	T-cell
Au et al., 2000	83, M	HA, visual loss	ant hypopit, DI	pituitary adenoma	B-cell
Mathiasen et al., 2000	65, M	muscle weakness, fatigue, decreased libido	ant hypopit, PRL	lymphocytic hypophysitis	B-cell
Singh et al., 2000	44, M	HA, visual loss, blurry vision, decreased libido	—	lymphocytic hypophysitis	B-cell
Spina et al., 2000	52, F	HA, diplopia (CN VI palsy)	ant hypopit, DI	lymphocytic hypophysitis	T-cell
Landman et al., 2001	86, F	fever, chills, weight loss	ant hypopit, DI	—	B-cell
Silfen et al., 2001	15, M	polyuria, polydipsia, weight loss	ant hypopit, DI	—	B-cell
Kaufmann et al., 2002	74, M	visual loss, mental status change, generalized weakness, weight loss	ant hypopit	—	B-cell
Katz et al., 2003	64, F	nausea/vomiting, diarrhea, peripheral & periorbital edema	ant hypopit, DI	—	B-cell
Huang et al., 2005	47, M	fever, chills, decreased libido	ant hypopit	lymphocytic hypophysitis	T-cell
present study	26, M	HA, diplopia (CN VI palsy), fever	ant hypopit, PRL	—	NK/T-cell

* ant hypopit = anterior hypopituitarism; CN = cranial nerve; DI = diabetes insipidus; HA = headache; PRL = hyperprolactinemia; SNHL = sensorineural hearing loss; — = none.

tained in the patient in our case showed stalk thickening and enhancement as well as dural enhancement in the anterior skull base and clivus, which are not typical imaging characteristics of pituitary adenomas, thereby suggesting a non-adenomatous lesion. Lymphomas usually appear iso- to hyperdense on CT imaging. On MR imaging, they are usually isointense on T1-weighted images and iso- to hypointense on T2-weighted images.^{17,20} They also usually show diffusion restriction (hyperintense on diffusion weighted images and hypointense on the apparent diffusion coefficient map), which reflects the hypercellular density of these tumors. Lymphomas almost always enhance homogeneously after Gd administration.⁵

Four patients had histological evidence of lymphocytic hypophysitis and two patients had underlying pituitary adenomas. Although the exact mechanism of pathogenesis of PPL remains unknown, some have postulated that lymphocytic hypophysitis and pituitary adenomas may be risk factors for acquiring pituitary lymphomas.^{11,13} One hypothesis is that a polyclonal population of inflammatory lymphocytes may undergo monoclonal expansion possibly triggered by an infectious agent. This may be analogous to the phenomenon seen in Hashimoto thyroiditis as a risk factor for developing thyroid lymphomas.¹ As for underlying pituitary adenomas, their role in the pathogenesis of PPL is unclear. Some authors have postulated that the combination of monoclonal expansion of lymphocytic infiltrates, expression of adenoma-specific signaling or adhesion molecules that attract circulating lymphocytes, and the mitogenic potential of some pituitary hormones may contribute to lymphoma growth within a pituitary adenoma.¹¹ In the present case, there was no evidence for a preexisting pituitary adenoma.

The majority of primary CNS tumors (98%) are monoclonal B-cell non-Hodgkin lymphomas.²⁰ Histologically, lymphomas of the pituitary gland resemble those of the CNS. Similar to primary CNS lymphomas, most are predominantly B-cell non-Hodgkin lymphoma. In our review of 18 patients with PPL, 13 (72%) were B-cell immunophenotype, four (22%) were T-cell immunophenotype, and one (6%) was NK/T-cell immunophenotype.

Extranodal NK/T-Cell Lymphoma

Extranodal NK/T-cell lymphomas are a rare group of invasive and destructive lymphoproliferative disorders that are immunophenotypically distinct from B-cell and T-cell non-Hodgkin lymphomas. They are derived from either activated NK cells or, rarely, cytotoxic T-cells. This tumor has been recently recognized as a distinct entity within the World Health Organization classification of hematopoietic and lymphoid neoplasms.⁴ The NK/T-cell lymphomas were previously known as lethal midline granuloma, polymorphic reticulosis, or angiocentric lymphoma. The incidence of these tumors is higher in Asia, Mexico, and South America.^{14,24} Within the US, NK/T-cell lymphomas comprise 1 to 2% of non-Hodgkin lymphomas.²² These lymphomas are commonly extranodal and usually arise within the nasal cavity as midfacial destructive lesions and present with nasal obstruction, facial pain, or swelling. Other extranasal sites of involvement, including the pharynx, gastrointestinal tract, and testis, have been described; tumors in these locations are also referred to as "nasal-type." Metastasis to the

CNS from nasal NK/T-cell lymphomas has been reported in less than 3% of cases;²² there has been one case reported of primary brain NK/T-cell lymphoma.¹⁵ To our knowledge, primary pituitary NK/T-cell lymphoma has not been previously reported. We report the first case of a nasal-type NK/T-cell lymphoma arising primarily in the pituitary gland with the classic immunophenotype.

Histologically, NK/T-cell lymphomas are often angiocentric with prominent necrosis and vascular destruction. Immunophenotypically, they typically express CD2 (T-cell marker), CD56 (NK cell marker), and intracellular cytoplasmic CD3 but lack surface CD3 expression. Other positive markers include cytotoxic granule proteins, granzyme B, TIA-1, and perforin.¹⁵ Another distinguishing feature of NK/T-cell lymphomas is the strong association with EBV, with EBER positivity in greater than 80% of cases.²²

Most cases of NK/T-cell lymphoma are aggressive and are associated with an unfavorable clinical outcome. Given the rarity of this disease, the optimal therapy has not been clearly defined. Treatment of nasal NK/T-cell lymphoma has consisted of radiotherapy, with or without multiagent chemotherapy;⁶ however, no effective treatment regimen has been yet elucidated, and this malignancy manifests an aggressive course. The highly aggressive course with poor response and short survival with standard therapies has led some investigators to recommend consolidation with bone marrow or peripheral stem cell transplantation.³

Ko et al.¹⁸ found that CD56-positive EBV-negative lymphomas at extranasal sites were clinically less aggressive and exhibited less necrosis than CD56-positive EBV-positive NK/T-cell lymphomas. The median survival time of all 47 patients in their series was 14 months, with a 2-year survival rate of 40%. The results of another study of 42 patients with nasal-type extranodal NK/T-cell lymphoma demonstrated a mean survival time of 30 months. In that study, younger female patients appeared to have longer survival times.²⁴ Unfortunately, systemic progression of this disease is common and, despite radiation therapy, surgery, and chemotherapy, poor outcomes prevail and death can occur within a year of diagnosis.²² In summary, NK/T-cell lymphoma is an aggressive tumor with a distinctive clinicopathological profile and an unfavorable clinical course, and, as demonstrated in the present report, it may rarely present as a pituitary mass.

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Primary pituitary lymphoma

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